

TRANSMITTAL LETTER TO THE UNITED STATES
DESIGNATED/ELECTED OFFICE (DO/EO/US)
CONCERNING A FILING UNDER 35 U.S.C. 371

525 Rec'd PGT/PTO 26 OCT 2000

U.S. APPLICATION NO. (If known, see 37 CFR 1.5)

09/674092

INTERNATIONAL APPLICATION NO.

PCT/US99/04359

INTERNATIONAL FILING DATE

February 26, 2000

PRIORITY DATE CLAIMED

TITLE OF INVENTION

CEREBROSPINAL AND VASCULAR PHARMACEUTICAL COMPOSITION AND PROCESS FOR PREPARING THE SAME

APPLICANT(S) FOR DO/EO/US

KEEP, Marcus; ELMER, Eskil

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39 (1).
4. ☐ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
 - a. ☒ is transmitted herewith (required only if not transmitted by the International Bureau). WO 00/50058
 - b. ☒ has been transmitted by the International Bureau.
 - c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(3)).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(2)).
 - a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
 - b. ☐ have been transmitted by the International Bureau.
 - c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
 - d. ☒ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern document(s) or information included:

11. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98./International Search Report with cited references
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☒ A **FIRST** preliminary amendment.
☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☒ Other items or information:

09/674092
526 Rec'd PCT/PTO 26 OCT 2000

PATENT
30-200P

IN THE U.S. PATENT AND TRADEMARK OFFICE

Applicant: KEEP et al.
Int'l. Appl. No.: PCT/US99/04359
Appl. No.: New Group:
Filed: October 26, 2000 Examiner:
For: CEREBROSPINAL AND VASCULAR
PHARMACEUTICAL COMPOSITION AND
PROCESS FOR PREPARING THE SAME

PRELIMINARY AMENDMENT

BOX PATENT APPLICATION

Assistant Commissioner for Patents
Washington, DC 20231

October 26, 2000

Sir:

The following Preliminary Amendments and Remarks are respectfully submitted in connection with the above-identified application.

AMENDMENTS

IN THE SPECIFICATION:

Please amend the specification as follows:

Before line 1, insert --This application is the national phase under 35 U.S.C. § 371 of PCT International Application No. PCT/US99/04359 which has an International filing date of February 26, 1999, which designated the United States of America.--

IN THE CLAIMS:

Please amend the claims as follows:

Claim 7, line 1, change "claims 3, 4, 5, and 6" to --claim 3--.

REMARKS

The specification has been amended to provide a cross-reference to the previously filed International Application.

The claims have been amended to reduce the number of multiple dependent claims and to improve the form thereof.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

By Joe McKinney Muncy
Joe McKinney Muncy, #32,334

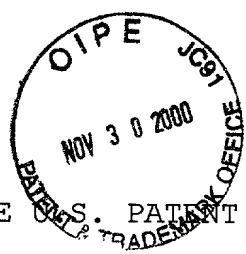
P.O. Box 747
Falls Church, VA 22040-0747
(703) 205-8000

KM/djm
30-200P

5630

526 Rec'd PCT/PTO 30 NOV 2000

PCT
09/674 092



PATENT
0030-0200P

IN THE U.S. PATENT AND TRADEMARK OFFICE

Applicant: KEEP, Marcus et al.
Appl. No.: 09/674,092 Group: UNASSIGNED
Filed: October 26, 2000 Examiner: UNASSIGNED
For: CEREBROSPINAL AND VASCULAR
PHARMACEUTICAL COMPOSITION AND PROCESS
FOR PREPARING THE SAME

5F00

ASSERTION OF SMALL ENTITY STATUS

Assistant Commissioner for Patents
Washington, DC 20231

November 30, 2000

Sir:

The above-identified application qualifies for small entity status. This written assertion of small entity status should satisfy the requirements of 37 C.F.R. § 1.27.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fee required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

By Joe McKinney Muncy
Joe McKinney Muncy, #32,334

KM/asc
0030-0200P

P.O. Box 747
Falls Church, VA 22040-0747
(703) 205-8000

0030-0200P

WO 00/50058

PCT/US99/04359

Cerebrospinal and vascular pharmaceutical composition
and process for preparing the same.

Description.

Field of the Invention:

This invention relates to pharmaceutical compositions that facilitate the administration of cyclosporins, particularly into cerebrospinal and vascular fluid spaces.

Background Art

Cyclosporin A and derivatives.

Cyclosporin A is an immunosuppressive drug. The above mentioned treatment medication has already been described, in United States Pat. No. 4,117,118 and numerous patents since, which relate to its production, formulation and immunosuppressive properties.

Cyclosporin A is a product of the fungus *Tolypocladium Inflatum* Gams. It is a cyclic poly-amino acid molecule, consisting of 11 amino acids. One of the amino acids is unique for cyclosporin A, a β -hydroxyamino acid called butenyl-methyl-threonin (MeBmt). The molecular weight is 1202.6 and the chemical composition is $C_{62}H_{111}N_{11}O_{12}$.

The molecule is highly lipophilic, and therefore virtually insoluble in water. The drug is transported in the blood within red blood cells to about 58%, and the remaining approximately 10-20% in leukocytes, and 33% bound to plasma proteins. In the plasma cyclosporin A is bound to high-density lipoprotein, low-density lipoproteins, very-low density lipoproteins and a small fraction to albumin. A very small fraction is free in plasma.

The drug undergoes extensive metabolism, mainly in the liver by the cytochrome P450 system. There are at least 30 known metabolites of cyclosporin A, with various chemical modifications, such as hydroxylation, demethylation, oxidation and epoxide formations. There are a number of variants of cyclosporin A, differing for example in one amino acid, which have similar pharmacological properties. Under normal conditions, cyclosporin A and its metabolites do not pass the blood-brain barrier. When the glycoprotein-p transporter is poisoned, or the blood-brain barrier is disrupted, cyclosporin is able to cross it and come into contact with neurons. Several analogs of cyclosporin are able to readily cross the blood-brain barrier. Several analogs of cyclosporin are not immunosuppressants. There is a subset of analogs of cyclosporin that both readily cross the blood-brain barrier and are not immunosuppressants.

The family of cyclosporins includes cyclosporin A, cyclosporin C, cyclosporin D, and cyclosporin G. Some known metabolites of cyclosporin A include the following : (according to Hawk's Cay nomenclature) AM1, AM9, AM1c, AM4N, AM19, AM1c9, AM1c4N9, AM1A, AM1A4N, AM1Ac, AM1AL, AM11d, AM69, AM4N9, AM14N, AM14N9, AM4N69, AM99N, Dihydro-CsA, Dihydro-CsC, Dihydro-CsD, Dibydro-CsG, M17, AM1c-GLC, sulphate conjugate of cyclosporin, BH11a, BH15a, B, G, E, (and with some overlap with the Hawk's above, according to Maurer's nomenclature) M1, M2, M3, M4, M5, M6, M7, M8, M9, M10, M11, M12, M13, M14, M15, M16, M17, M18, M19, M20, M21, M22, M23, M24, M25, M26, MUNDF1 and McBMT. Some metabolites of cyclosporin G include GM1, GM9, GM4N, GM1c, GM1c9, and GM19. Modified cyclosporins include modified C-9 amino acid analogs, modified 8-amino acid analogs, modified 6-position analogs containing MeAla or MeAbu residue, and SDZ 209-313, SDZ-205-549, SDZ-033-243, and SDZ-PSC-833.

This entire family of cyclosporins, including cyclosporin A, all derivatives, variants, amino acid variants, metabolites, including variations of mono-, di- and trihydroxylates, N-demethylates, aldehydes, carboxylates, conjugates, sulphates, glucuronides, intramolecular cyclizations and those without a cyclic structure as well as shorter peptides and amino acids and their derivatives and salts with or without immunosuppressive properties and whether able to cross the blood brain barrier or not will hereinafter be referred to as cyclosporin or cyclosporins.

Cyclosporins are highly lipophilic and virtually insoluble in water. They require an emulsifier to remain in aqueous phase, such as cremophore or Labrafil. One problem is that these emulsifiers are anaphylactic, and are neurotoxic. There is a need for an improved formulation for intravenous and oral use that is neither anaphylactic nor neurotoxic.

Further no formulation in existence is suitable for injection into the cerebrospinal fluid or the brain because of the neurotoxic and irritant properties of the emulsifiers. No formulation now exists which is used for cerebrospinal administration.

Therefore our aim was to create a unique cerebrospinal pharmaceutical composition with cyclosporin as the active ingredient that does not contain dangerous neurotoxic emulsifiers and irritants found in vascular and oral formulations.

Now we have found that if cyclosporin is dissolved in DMSO (dimethyl sulfoxide), the neurotoxic and irritant effects on the nervous system are not seen. Further we have found that not only is it a unique new cerebrospinal fluid composition with great safety and free from neurotoxicity, but that it is also an improved formulation for intravascular and oral administration too.

DMSO

Dimethyl sulfoxide is an industrial solvent derived from wood. It is biocompatible, but approved in only one condition for human use, that of interstitial cystitis, a completely unrelated bladder condition. DMSO may by itself be useful for other conditions such as scleroderma, arthritis, mental illness, and brain trauma, but is not accepted into general medical use for these conditions.

The Instant Invention.

Cyclosporins are highly lipid soluble. There are well known to the art a number of mixtures for oral and intravenous administration, usually involving a carrier solution of lipid in water emulsion, micro-emulsion or nano-emulsion or particles. For intravenous administration this lipid in water emulsion is designed to allow administration in fluid phase mixed with salt-water solution to allow easy flow without precipitation of cyclosporin in the administering tubing or the blood. This has been acceptable in the past for simple intravenous (or oral) administration at the relatively low doses needed to treat immune rejection in transplantation or autoimmune disease.

It has been recently discovered that cyclosporin is neuroprotective when it comes into contact with neurons. Since the drugs are also systemically immunosuppressive, it would be desirable to administer them selectively into the brain or the cerebrospinal fluid around the brain. Nonsystemic local CSF administration of cyclosporin would reduce systemic immune suppression, and increase brain and spine neuron exposure compared to systemic administration, both very desirable goals in patients in need of neuroprotection but not in need of immunosuppression. Especially patients that need long term treatment neuroprotection (such as those with amyotrophic lateral sclerosis, Parkinson's disease and Alzheimer's disease), it is desirable to avoid the complication, or undesirable side effect of lifelong systemic immunosuppression.

Lipids emulsifiers are used in Sandimmune (Novartis' formulation for cyclosporin) such as a modified castor oil derivative (Labrafil and cremophore). These castor oil derivatives have been themselves found to be directly neurotoxic, and likely to be the cause of the reported cases of neurologic problems of encephalopathy, and seizures in transplant patients.

Other formulations use less neurotoxic lipid formulations such as tocerafols. However lipids injected into the cerebrospinal fluid have been reported to cause severe complications of arachnoiditis or inflammation around the spinal cord-such as the discontinued oil based Pantopaque intrathecal X-ray contrast used in spinal myelograms. Injecting lipids, even in micro or nano-emulsions into the cerebrospinal spaces would likely cause layering of the lipid, since the long column of fluid in the spine contains slow moving CSF, which is a very different milieu than the rapidly

flowing and mixing turbulent arterial and venous blood. The layering of lipid and drug in the cerebrospinal fluid column would result in undesirable cyclosporin over or underdosage, depending on location.

In addition, ethanol is a commonly used solvent for cyclosporin used in Sandimmune and SangCya (Sangstat's cyclosporin formulation). Ethanol is a known neurotoxin, and is used for neurolysis or destruction of nerve roots by injection into the brain or cerebrospinal fluid spaces.

It is now found to be desirable to inject cyclosporin into the fluid contained within the brain, and in which the brain floats, the cerebrospinal fluid. Clearly all previously described oral preparations, and all previously described intravenous preparations are not suitable because they contain neurotoxins and irritants as solvents or emulsifiers. In addition the known intravenous formulations are not ideal for intravenous use because they contain neurotoxins which causes the documented manifestations of neurotoxicity in patients obtaining intravenous or oral administration. Cerebrospinal injections of these intravenous formulations would cause unacceptable and potentially lethal neurotoxic effects.

All previous formulations for cyclosporin have utilized a lipid emulsifier to obtain solubility. It would not be expected by a person skilled in the art that a completely different class of compound other than a lipid emulsifier, such as the industrial solvent DMSO would turn out to be suitable for intracerebrospinal administration. Further they would not expect that the use of an industrial solvent would be an improvement over existing intravascular and oral cyclosporin compositions.

This novel formulation for administering cyclosporin into the CSF is the use of dimethylsulfoxide (DMSO) as the carrier medium or solvent. Cyclosporin is very soluble in DMSO. Unlike castor oil derivatives or ethanol, DMSO is not neurotoxic. It is highly biocompatible and is actually a known neuroprotectant in its own right. It is possible to safely administer DMSO. DMSO prevents precipitation of cyclosporin even when diluted in the CSF.

In addition DMSO easily crosses tissues barriers in its role as a solvent and carries in with it drugs dissolved in it. This is an advantage because it opens the blood-brain barrier and CSF-brain barrier to facilitate cyclosporin penetration into the brain.

The two main methods for infusing the formulation will be via the cerebral ventricles and the thecal sac. A catheter placed through a scalp incision, a skull twist drill hole and the brain, will access the cerebral ventricles. If a short-term infusion of several days is desired the catheter would be remain externalized and then removed. If a long term infusion over months or years were desired, the skin would be closed over the catheter and an attached refillable reservoir or drug pump.

Thecal sac infusion is typically by lumbar puncture in the lumbar spine (or less often at the top of the spine at the base of the skull). The spinal puncture needle is placed through the skin of the back and pierces the dura (thecal sac) which contains the CSF in which the spinal cord is floating. Once in, formulary drug can be infused into the CSF in one session via the needle, or over a week through a soft catheter. For long term infusion over months or years, the soft catheter is connected under the skin to a refillable programmable pump that is usually implanted under the abdominal skin.

In addition to being a novel, unique, efficacious and safe formulation for intrathecal administration, this formulation is also superior for intravenous or intra-arterial administration. The absence of systemic neurotoxic castor oil derivatives will reduce the well-known neurological complications. The tissue penetrating capabilities of DMSO will facilitate penetration of the blood-brain barrier by cyclosporin to come into contact with neurons to make it work better.

Medicament and administration.

The formulary drug can be administration by the routes including oral, sublingual, buccal, nasal, inhalation, parenteral (including intraperitoneal, intraorgan, subcutaneous, intradermal, intramuscular, intra-articular, venous (central, hepatic or peripheral), lymphatic, cardiac, arterial, including selective or superselective cerebral arterial approach, retrograde perfusion through cerebral venous system, via catheter into the brain parenchyma or ventricles), direct exposure or under pressure onto or through the brain or spinal tissue, or any of the cerebrospinal fluid ventricles, injections into the subarachnoid, brain cisternal, subdural or epidural spaces, via brain cisterns or lumbar puncture, intra and peri-ocular instillation including application by injection around the eye, within the eyeball, its structures and layers, as well as via enteral, bowel, rectal, vaginal, urethral or bladder cisternal. Also for *in utero* and perinatal indications then injections into the maternal vasculature, or through or into maternal organs including the uterus, cervix and vagina, and into embryo, fetus, neonate and allied tissues and spaces such as the amniotic sac, the umbilical cord, the umbilical artery or veins and the placenta, with parenteral being the preferred route.

The formulary drug, containing cyclosporin dissolved in DMSO, for administration into the brain and related structures, spinal cord and related structures, ventricular system and cerebrospinal fluid spaces can be manufactured and distributed containing, aqueous and non-aqueous injection solutions, other pharmaceutically active compounds, additives including anti-oxidants, bacteriostats and solutes and sugars such as mannitol to make the formulary drug isotonic, hypotonic or hypertonic with the cerebrospinal fluid; and also aqueous and non-aqueous sterile suspensions. The formulary drug can be manufactured and distributed in unit-dose or multi-dose containers, such as sealed glass or plastic ampoules, vials, bottles and bags as a liquid, and in a dry state requiring the addition of DMSO.

The formulary drug for parenteral administration can be manufactured from cyclosporin, DMSO, aqueous sterile injection solutions, other pharmaceutically active compounds, additives including anti-oxidants, bacteriostats and solutes and sugars such as mannitol to make the formulary drug isotonic, hypotonic or hypertonic with the fluids of the recipient. The formulary drug can be manufactured and distributed in unit-dose or multi-dose containers, such as sealed glass or plastic ampoules, vials, bottles and bags as a liquid, and in a dry state requiring the addition of DMSO.

The formulations are used in patients who require neuroprotection from neurological diseases of acute to chronic nature including stroke, brain hemorrhage, brain and spine trauma, ionizing radiation, neurotoxicity to vestibulocochlear structures, retinal detachment and neurodegeneration including amyotrophic lateral sclerosis, Parkinson's and Alzheimer's.

The formulations are used in patients who require both neuroprotection from neurological disease and that their neuro-axis be immunocompromised, such as in neural transplantation, neural xenotransplantation, multiple sclerosis, HIV neuropathy and Guillain-Barré syndrome.

The formulations are used in patients who require that they be immunocompromised, such as in transplantation and autoimmune disease.

The formulations are used for topical application for patients who require immunocompromise of the skin for diseases such as psoriasis.

The formulary drug generally contains from 0.1 to 90% of the treatment medication by weight of the total composition. Cerebrospinal doses between 5 mg and 5 gram per day are possible, with about 50-150 mg/day for chronic administration, and 100-1000 mg/day for acute administration being preferable. Amounts of from 0.0001 mg to 200 mg/kg, or preferably 0.001 to 50 mg/kg, of body weight per day for parenteral administration and 0.001 to 150 mg/kg orally, can be given. Nevertheless, it could be necessary to alter those dosage rates, depending on the condition, weight, and individual reaction of the subject to the treatment, and the mode in which the administration is carried out, and the stage of the disease process or interval of administration. It may thus be sometimes adequate to use less than the before stated minimum dose, while in other instances the upper limit must be surpassed to obtain therapeutic results.

Examples:**Example 1**

Sterile Injectable Concentrate Formulary Drug with cyclosporin as active ingredient

Containing per ml:

Cyclosporin A	200	mg
DMSO	800	mg

The formulary drug is made by dissolving 5 grams of cyclosporin into 20 grams dimethyl sulfoxide at room temperature. The solution thus obtained is made up to 25 ml with water. The solution is homogenized with stirring and filtered. The liquid is sterilized by radiation and then placed in a sealed container such as glass under inert gas atmosphere in doses of 1, 5 or 25 ml.

Sterile injectable concentrate formulary drug is administered, with or without dilution with for example isotonic saline, by infusion or by injection into cerebrospinal fluid spaces, brain, spine, vein or artery.

Example 2

A person in need of acute brain or spinal neuroprotection from trauma or stroke has the composition of example 1 injected into the cerebrospinal fluid of the ventricle of the brain through a burrhole in the skull, or into the cerebrospinal fluid of thecal sac via a lumbar puncture needle, or injected intravascularly.

Example 3

A person in need of chronic brain or spinal neuroprotection from neurodegenerative disease such as Parkinson's, Alzheimer's or amyotrophic lateral sclerosis has the composition of example 1 injected periodically by a reservoir or pump into the cerebrospinal fluid of a brain ventricle through a burrhole in the skull, or into the cerebrospinal fluid of the thecal sac via a lumbar catheter connected to a reservoir and pump.

Example 4

A person in need of neural immunosuppression for neural transplantation, neural xenotransplantation, or diseases with autoimmune components like multiple sclerosis, Guillain-Barré, has the composition of example 1 injected periodically by a reservoir or pump into the cerebrospinal fluid of a ventricle of the brain through a burrhole in the skull, or into the cerebrospinal fluid of the spinal thecal sac via a lumbar catheter connected to a reservoir and pump.

Example 5

A person in need of systemic immunosuppression has intravenous injections or oral consumption of the compositions of examples 1.

Industrial Applicability

From the above description it will be evident that the present invention provides improved compositions for the administration of cyclosporin. Additionally the present invention provides a completely new composition suitable for administration directly into the new target of delivery, the cerebrospinal fluid to directly treat diseases of the brain, which previously described compositions are not suitable for, because of the neurotoxicity of their solvents.

No precipitation was observed with an initial one month of testing of composition prepared according to example 1. Ampoules stored in darkness containing 5 ml stored at 0, 30, and 60 degrees C show neither discoloration nor precipitation.

Rats receiving intraventricular cerebrospinal infusions showed no neurotoxicity, seizures or untoward effects. In addition, rats receiving injections intravenously showed no ill effects.

Claims: What is claimed is:

1. A pharmaceutical composition of matter in the form of a solution concentrate comprising a cyclosporin dissolved in DMSO.
2. A composition as in claims 1 wherein the cyclosporin is cyclosporin A.
3. A method for administering cyclosporin into cerebrospinal fluid spaces, including intraventricular and intrathecal, in a patient, the improvement which comprises: providing cyclosporin dissolved in DMSO in a pharmaceutically acceptable carrier, and administering said cyclosporin and DMSO solution by injection into the cerebrospinal fluid spaces to said patient.
4. A method for administering cyclosporin by injection including intra-ocular, intravestibular, into or adjacent to the brain, or spinal cord into a patient, the improvement which comprises: providing cyclosporin dissolved in DMSO in a pharmaceutically acceptable carrier, and administering said cyclosporin and DMSO solution by injection intra-ocular, intravestibular, into or adjacent to the brain, or spinal cord to said patient.
5. A method for administering cyclosporin by injection including intravenous, intra-arterial or intraparenchymal, into a patient, the improvement which comprises: providing cyclosporin dissolved in DMSO in a pharmaceutically acceptable carrier, and administering said cyclosporin and DMSO solution by injection into intravenous, intra-arterial or intraparenchymal spaces to said patient.
6. A method for administering cyclosporin orally, rectally, nasally or dermally to a patient, the improvement which comprises: providing the cyclosporin dissolved in DMSO in a pharmaceutically acceptable carrier, and administering said cyclosporin and DMSO solution orally, rectally, nasally or dermally to said patient.
7. The method of claims 3,4,5, and 6 wherein the cyclosporin is cyclosporin A, or functional derivatives, metabolites, variants or salts thereof.
8. An article of manufacture comprising packaging material and pharmaceutical agent contained within said packaging material, wherein the pharmaceutical agent is therapeutically effective for reducing or preventing neuronal damage and for causing immunosuppression when administered in a therapeutically effective quantity, and wherein the packaging material comprises a label which indicates that the pharmaceutical agent can be used for reducing or preventing neuronal damage and for causing immunosuppression, and wherein said pharmaceutical agent comprises DMSO and a cyclosporin such as cyclosporin A or a compound of the class of cyclosporins, or functional derivatives, metabolites, variants or salts of them thereof, or combination of the before said, either alone or in admixture with diluents, or additives

BIRCH, STEWART, KOLASCH & BIRCH, LLPP.O. Box 747 • Falls Church, Virginia 22040-0747
Telephone: (703) 205-8000 • Facsimile: (703) 205-8050PLEASE NOTE:
YOU MUST
COMPLETE THE
FOLLOWING**COMBINED DECLARATION AND POWER OF ATTORNEY
FOR PATENT AND DESIGN APPLICATIONS**

As a below named inventor, I hereby declare that: my residence, post office address and citizenship are as stated next to my name; that I verily believe that I am the original, first and sole inventor (if only one inventor is named below) or an original, first and joint inventor (if plural inventors are named below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

**CEREBROSPINAL AND VASCULAR PHARMACEUTICAL COMPOSITION AND
PROCESS FOR PREPARING THE SAME**

Insert Title:

Fill in Appropriate
Information -
For Use Without
Specification
Attached:

the specification of which is attached hereto. If not attached hereto,

the specification was filed on _____ as

United States Application Number 09/674,092 _____;

and amended on _____ (if applicable) and/or

the specification was filed on October 26, 2000 as PCTInternational Application Number PCT/US99/04359 _____; and was

amended under PCT Article 19 on _____ (if applicable)

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

I do not know and do not believe the same was ever known or used in the United States of America before my or our invention thereof, or patented or described in any printed publication in any country before my or our invention thereof or more than one year prior to this application, that the same was not in public use or on sale in the United States of America more than one year prior to this application, that the invention has not been patented or made the subject of an inventor's certificate issued before the date of this application in any country foreign to the United States of America on an application filed by me or my legal representative or assigns more than twelve months (six months for designs) prior to this application, and that no application for patent or inventor's certificate on this invention has been filed in any country foreign to the United States of America prior to this application by me or my legal representatives or assigns, except as follows.

I hereby claim foreign priority benefits under Title 35, United States Code, §119(a)-(d) of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s)**Priority Claimed**

(Number) _____	(Country) _____	(Month/Day/Year Filed) _____	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
(Number) _____	(Country) _____	(Month/Day/Year Filed) _____	<input type="checkbox"/> Yes	<input type="checkbox"/> No
(Number) _____	(Country) _____	(Month/Day/Year Filed) _____	<input type="checkbox"/> Yes	<input type="checkbox"/> No
(Number) _____	(Country) _____	(Month/Day/Year Filed) _____	<input type="checkbox"/> Yes	<input type="checkbox"/> No

I hereby claim the benefit under Title 35, United States Code, §119(e) of any United States provisional applications(s) listed below.

(Application Number) _____	(Filing Date) _____
(Application Number) _____	(Filing Date) _____

All Foreign Applications, if any, for any Patent or Inventor's Certificate Filed More than 12 Months (6 Months for Designs) Prior to the Filing Date of This Application:

Country	Application Number	Date of Filing (Month/Day/Year)
_____	_____	_____
_____	_____	_____

I hereby claim the benefit under Title 35, United States Code, §120 of any United States and/or PCT application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States and/or PCT application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose information which is material to the patentability as defined in Title 37, Code of Federal Regulations, §1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

<u>PCT/US99/04359</u>	<u>February 26, 1999</u>	_____
(Application Number)	(Filing Date)	(Status - patented, pending, abandoned)
(Application Number) _____	(Filing Date) _____	(Status - patented, pending, abandoned)

Prior U.S.
Application(s):
(y)

I hereby appoint the following attorneys to prosecute this application and/or an international application based on this application and to transact all business in the Patent and Trademark Office connected therewith and in connection with the resulting patent based on instructions received from the entity who first sent the application papers to the attorneys identified below, unless the inventor(s) or assignee provides said attorneys with a written notice to the contrary.

Raymond C. Stewart
Joseph A. Kolasch
Bernard L. Sweeney
Charles Gorenstein
Leonard R. Svensson
Andrew D. Meikle
Joe McKinney Muncy
John W. Bailey
Gary D. Yacura

(Reg. No. 21,066)
(Reg. No. 22,463)
(Reg. No. 24,448)
(Reg. No. 29,271)
(Reg. No. 30,330)
(Reg. No. 32,868)
(Reg. No. 32,334)
(Reg. No. 32,881)
(Reg. No. 35,416)

Terrell C. Birch
James M. Slattery
Michael K. Mutter
Gerald M. Murphy, Jr.
Terry L. Clark
Marc S. Weiner
Donald J. Daley
John A. Castellano

(Reg. No. 19,382)
(Reg. No. 28,380)
(Reg. No. 29,680)
(Reg. No. 28,977)
(Reg. No. 32,644)
(Reg. No. 32,181)
(Reg. No. 34,313)
(Reg. No. 35,094)

Send Correspondence to:

BIRCH, STEWART, KOLASCH & BIRCH, LLP

or


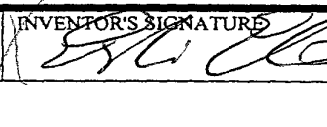
Customer No. 2292

P.O. Box 747 • Falls Church, Virginia 22040-0747

Telephone: (703) 205-8000 • Facsimile: (703) 205-8050

PLEASE NOTE:
YOU MUST
COMPLETE
THE
FOLLOWING:

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full Name of First or Sole Inventor Insert Name of Inventor Insert Date Filed Document is Signed Insert Residence Insert Citizenship Insert Post Office Address	GIVEN NAME/FAMILY NAME Marcus KEEP		INVENTOR'S SIGNATURE 	DATE* 13 Feb '01
	Residence (City, State & Country) Honolulu, HI, U.S.A.		CITIZENSHIP American	
	POST OFFICE ADDRESS (Complete Street Address including City, State & Country) Suite 208, 2228 Lilina Street, Honolulu, HI, 96817, U.S.A.			
Full Name of Second Inventor, if any see above	GIVEN NAME/FAMILY NAME Eskil ELMER		INVENTOR'S SIGNATURE 	DATE* 13 Feb 01
	Residence (City, State & Country) Lund, Sweden		CITIZENSHIP Swedish	
	POST OFFICE ADDRESS (Complete Street Address including City, State & Country) Partenas Grande 57, S-226 47 Lund, Sweden			
Full Name of Third Inventor, if any see above	GIVEN NAME/FAMILY NAME		INVENTOR'S SIGNATURE	DATE*
	Residence (City, State & Country)		CITIZENSHIP	
	POST OFFICE ADDRESS (Complete Street Address including City, State & Country)			
Full Name of Fourth Inventor, if any see above	GIVEN NAME/FAMILY NAME		INVENTOR'S SIGNATURE	DATE*
	Residence (City, State & Country)		CITIZENSHIP	
	POST OFFICE ADDRESS (Complete Street Address including City, State & Country)			
Full Name of Fifth Inventor, if any see above	GIVEN NAME/FAMILY NAME		INVENTOR'S SIGNATURE	DATE*
	Residence (City, State & Country)		CITIZENSHIP	
	POST OFFICE ADDRESS (Complete Street Address including City, State & Country)			